

corrections of grammatical or typographical errors, or text originally included as part of the now-removed drawing figures and inserted into the Brief Description of the Drawings. Deletions are made in brackets, and additions are underlined. No new matter has been added.

AMENDMENTS

In the Specification:

The following amendments to the Specification have been made in the above-referenced Substitute Specification.

Page 1, lines 4-5, the text "docket no. IFT 5657 CIP 2 (1417Y P606)" has been replaced with - serial number 10/035,821;

Page 1, line 6, "application are" has been changed to - applications which are--.

Page 2, line 29, an extra close bracket ")" has been deleted;

Page 2, line 31, "In U.S." has been changed to - United States--, and "4,752,442 which" has been changed to - 4,752,442--;

Page.3, line 6, "U.S." has been changed to - United States--;

Page 3, line 13, "U.S." has been changed to - United States - - and "Nos." has been changed to - No.--.

Page 6, line 7, "presuspension" has been changed to - pre-suspension--;

Page 6, line 10, "presuspension" has been changed to - pre-suspension--;

Page 6, line 18, "presuspension" has been changed to - pre-suspension--;

Page 6, line 19, the following paragraph has been inserted:

-- These and other aspects and attributes of the present invention will be discussed with reference to the following drawings and accompanying specification.--

Page 6, line 22, "Not Applicable. The Drawings have been incorporated into the text" has been deleted and replaced with the following:

- Figure 1 shows a diagrammatic representation of one method of the present invention;
Figure 2 show a diagrammatic representation of another method of the present invention;

Figure 3 shows amorphous particles prior to homogenization;
Figure 4 shows particles after annealing by homogenization;
Figure 5 is an X-Ray diffractogram of microprecipitated itraconazole with polyethylene glycol-660 12-hydroxystearate before and after homogenization;
Figure 6 shows Carbamazepine crystals before homogenization;
Figure 7 shows Carbamazepine microparticulate after homogenization (Avestin C-50);
Figure 8 is a diagram of illustrating the Microprecipitation Process for Prednisolone;
Figure 9 is a photomicrograph of prednisolone suspension before homogenization;
Figure 10 is a photomicrograph of prednisolone suspension after homogenization;
Figure 11 illustrates a comparison of size distributions of nanosuspensions (this invention) and commercial fat emulsion;
Figure 12 shows the X-ray powder diffraction patterns for raw material itraconazole (top) and SMP-2-PRE (bottom). The raw material pattern has been shifted upward for clarity;
Figure 13a shows the DSC trace for raw material itraconazole;
Figure 13b shows the DSC trace for SMP-2-PRE;
Figure 14 illustrates the DSC trace for SMP-2-PRE showing the melt of the less stable polymorph upon heating to 160°C, a recrystallization event upon cooling, and the subsequent melting of the more stable polymorph upon reheating to 180°C;
Figure 15 illustrates a comparison of SMP-2-PRE samples after homogenization. Solid line = sample seeded with raw material itraconazole. Dashed line = unseeded sample. The solid line has been shifted by 1 W/g for clarity;
Figure 16 illustrates the effect of seeding during precipitation. Dashed line = unseeded sample, solid line = sample seeded with raw material itraconazole. The unseeded trace (dashed line) has been shifted upward by 1.5 W/g for clarity; and
Figure 17 illustrates the effect of seeding the drug concentrate through aging. Top x-ray diffraction pattern is for crystals prepared from fresh drug concentrate, and is consistent with the stable polymorph (see Figure 12, top). Bottom pattern is for crystals prepared from aged (seeded) drug concentrate, and is consistent with the metastable polymorph (see Figure 12, bottom). The top pattern has been shifted upward for clarity. --

Page 8, line 20, "presuspension" has been changed to - - pre-suspension--;

Page 8, line 24, "presuspension" has been changed to - - pre-suspension--.

Page 9, line 21-22, "shown diagrammatically below" has been changed to - - shown diagrammatically in Figures 1 and 2 respectively--;

Page 9, line 23, "Figure 1: Method A:" has been deleted, as well as the associated figure 1 on the top of page 10.

Page 10, "Figure 2: Method B:" has been deleted, as well as the associated figure 2.

Page 12, line 33, "Tweens.TM." has been changed to - -TweensTM--.

Page 16, line 30, "presuspension" has been changed to - - pre-suspension--.

Page 17, lines 8-9, "presuspension" has been changed to - - pre-suspension--;

Page 17, line 13, "presuspension" has been changed to - - pre-suspension--;

Page 17, lines 18-19, "presuspension" has been changed to - - pre-suspension--;

Page 17, line 27, "presuspension" has been changed to - - pre-suspension--;

Page 17, line 30, "presuspension" has been changed to - - pre-suspension--.

Page 18, line 15, "presuspension" has been changed to - - pre-suspension--;

Page 18, line 31, "presuspension" has been changed to - - pre-suspension--.

Page 19, line 8, "presuspension" has been changed to - - pre-suspension--;

Page 19, line 9, "presuspension" has been changed to - - pre-suspension--;

Page 19, line 13, "presuspension" has been changed to - - pre-suspension--.

Page 20, line 28, "Figure 3: Amorphous particles prior to homogenization (Example 1)." has been deleted, as well as the associated figure on the top of page 21.

Page 21, "Figure 4: Particles after annealing by homogenization." has been deleted, as well as the associated figure following.

Page 26, lines 1-2, "Figure 5: X-Ray diffractogram of microprecipitated itraconazole with polyethylene glycol-660 12-hydroxystearate before and after homogenization (Example 5)." and the associated figure has been deleted.

Page 26, line 12, "2.44 um" has been changed to - - 2.44 μ m--.

Page 28, line 21, "Figure 6: Carbamazepine crystals before homogenization (Example 6)." and the associated figure have been deleted.

Page 29, line 1, "Figure 7: Carbamazepine microparticulate after homozenization (Avestin C-50)" and the associated figure have been deleted;

Page 29, line 2, "(Example 6)." has been deleted.

Page 31, line 6, "Figure 8: Diagram of Microprecipitation Process for Prednisolone (Examples 9-12)" has been deleted, as well as the associated figure;

Page 31, lines 10-11, "Figure 9: Photomicrograph of prednisolone suspension before homogenization (Hoffman Modulation Contrast, 1250X magnification)" has been deleted, as well as the associated figure on the top of page 32.

Page 32, "Figure 10: Photomicrograph of prednisolone suspension after homogenization (Hoffman Modulation Contrast, 1250X magnification). has been deleted, as well as the associated figure.

Page 33, line 21, "0.927 um" has been changed to - - 0.927 μ m--, and "2.36 um" has been changed to - - 2.36 μ m--.

Page 34, line 30, a period has been added after the end of the sentence.

Page 36, lines 1-2, "Figure 11: Comparison of size distributions of nanosuspensions (this invention) and commercial fat emulsion. (Example 13)" has been deleted, as well as the associated figure.

Page 37, line 21, "2-3⁰C" has been changed to --2-3⁰C--;

Page 37, line 25, "25⁰C" has been changed to --25⁰C--;

Page 37, line 29, "0.02⁰" has been changed to --0.02⁰-- and "0.25⁰" has been changed to --0.25⁰--.

Page 38, line 4, "2⁰/min to 180⁰C" has been changed to --2⁰/min to 180⁰C--;

Page 38, line 7, "165⁰C" has been changed to --165⁰C--;

Page 38, line 9, "159⁰C" has been changed to --159⁰C-- and "153⁰C" has been changed to --153⁰C--;

Page 38, line 21, "30⁰C" has been changed to --30⁰C--;

Page 38, line 23, "30⁰C" has been changed to --30⁰C--;

Page 38, line 25, "2⁰/min to 180⁰C" has been changed to --2⁰/min to 180⁰C--.

Page 39, line 5, "3⁰C" has been changed to --3⁰C--;

Page 39, line 9, "30⁰C" has been changed to --30⁰C--;

Page 39, lines 11-12, "2⁰/min to 180⁰C" has been changed to --2⁰/min to 180⁰C--;

Page 39, line 27, "presuspension" has been changed to - - pre-suspension--.

Page 40, line 4, "presuspension" has been changed to - - pre-suspension--;

Page 40, Figure 12, and associated text on top of page 41 has been deleted.

Page 41, Figure 13a, and associated text has been deleted.

Pages 42, 43, and 44 have been deleted in entirety (i.e., figures 13b, 14, 15, 16, and associated text).

Page 45, Figure 17 and associated text has been deleted.

In the claims:

Claim 61, line 2, "presuspension" has been changed to - - pre-suspension--.

Claim 63, line 1, "presuspension" has been changed to - - pre-suspension--.

Claim 64, line 1, "presuspension" has been changed to - - pre-suspension--.

Claim 65, line 1, "presuspension" has been changed to - - pre-suspension--.

Claim 76, line 2, "about 11" has been changed to - -about 11--.

Claim 98, line 7, "presuspension" has been changed to - - pre-suspension--; and line 9, "presuspension" has been changed to - - pre-suspension--.

Claim 100, line 2, "presuspension" has been changed to - - pre-suspension--.

Claim 101, line 2, "presuspension" has been changed to - - pre-suspension--.

Claim 102, line 2, "presuspension" has been changed to - - pre-suspension--.

Claim 103, line 2, "presuspension" has been changed to - - pre-suspension--.

Claim 104, lines 1-2, "presuspension" has been changed to - - pre-suspension--; and lines 2-3, "presuspension" has been changed to - - pre-suspension--.

Claim 112, lines 1-2, "presuspension" has been changed to - - pre-suspension--.

In the Abstract:

Line 7, "presuspension" has been changed to - - pre-suspension--.

Other minor changes, such as removing or adding spaces between words for readability have been effected, but have not been individually noted in this communication.

CONCLUSION

Applicants respectfully submit that the specification and drawings are now in formal condition, and with the submission of the executed Declaration and Power of Attorney and payment of the required filing fees and extension fees, this application can now proceed to examination.

The Examiner is invited to contact the undersigned directly if there be any questions in this matter.

Respectfully submitted,
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